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EXAMINER

CROWDER, CHUN

ART UNIT PAPER NUMBER

1644

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/660,301

Applicant(s)

GIROIR ET AL.

Examiner

Chun Crowder

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09/10/2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's Appeal Brief, filed on 09/10/2006, is acknowledged. Upon reconsideration, New Grounds of Rejection are set forth below. PROSECUTION IS HEREBY REOPENED.

The Examiner apologizes for any inconvenience in this matter.

2. Claims 1-19 are pending and currently under consideration.

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Applicant is required to identify the written support for claims 11-14, particularly the claimed limitation of "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values".

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-6 are indefinite in the recitation of "a person not predetermined to be subject to cardiovascular disease" because the metes and the bounds of the phrase is unclear and ambiguous. The term is neither defined by the claims nor by the instant specification. The specification disclosed the phrase on Summary of the Invention on page 2, however, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the invention.

B) Claims 1-7 are indefinite in the recitation of “cardiovascular risk metric” because the metes and the bounds of the phrase is unclear and ambiguous. The term is neither defined by the claims nor by the instant specification. The specification disclosed the term on Summary of the Invention on page 2, however, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the claimed “cardiovascular risk metric”.

C) Claims 7-14 and 17 are indefinite in the recitation of “apparently healthy individual” and “the individual is apparently healthy”, respectively because the metes and bounds of the phrase are unclear and ambiguous. The phrases are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the invention. It is not clear what constitutes “apparently healthy individual” and “the individual is apparently healthy”.

The instant specification on page 3 discloses that “an apparently healthy individuals” have not previously had an acute adverse cardiovascular event and generally do not otherwise exhibit symptoms of disease, particularly acute disease. However, it is not clear what constitutes symptoms of disease, particularly acute disease.

D) Claims 11-14 are indefinite in the recitation of “characterizing the individual’s risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values” because the metes and bounds of the claims are unclear and ambiguous. The phrase is not defined by the claims and the specification does not have support for the claimed limitations, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the invention.

E) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-19 are drawn to a method of determining cardiovascular risk in a person not predetermined to be subject to cardiovascular disease, and/or apparently healthy individual, the method comprising the step of determining a test microphage migration inhibitory factor (MIF) concentration as a marker of cardiovascular risk for the person wherein the elevated MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicated that the person is subject to elevated cardiovascular risk.

The specification discloses that MIF is elevated in adults with high cardiovascular risk, and that serum MIF falls with reduction in cardiovascular risk (see Detailed Description of the Invention on pages 2-6 of the instant specification). The specification further discloses that the level of MIF is a predicative marker of future cardiovascular disorder in apparently healthy but statistically or professionally determined overweight or obese persons, and/or are subject to or predisposed to type II diabetes.

However, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is not clear whether MIF can be used as a marker for cardiovascular risk for any person not predetermined to be subject to cardiovascular disease and/or an apparently healthy individual as broadly claimed by the instant application. The specification as filed discloses examples to show that MIF levels were 38 ± 16 ng/ml in the control group while MIF is 100 ng/ml in obese patients and generally drop to normal levels after 1 year (see Examples on pages 5-6 of the instant specification). However, it is not clear what population is encompassed in a control group (age, sex etc).

The state of the art (Pan et al. J Vasc Surg 2003. 37:628-635) recognizes that MIF is a pleiotropic cytokine released from macrophages, T lymphocytes, and the pituitary gland during inflammatory responses, high serum MIF levels have been described in a variety of diseases such as rheumatoid arthritis, sepsis, asthma, and uveitis malarial anemia, glomerulonephritis, chronic colitis, and multiple sclerosis (see entire document, particularly page 628 and page 632). Thus, higher MIF concentration in patients with rheumatoid arthritis, sepsis, asthma, and uveitis would not necessarily be associated with cardiovascular risk.

Further, the selection of appropriate controls and the interpretation of their results can be controversial, for example, a proper control group needs to be gender and age matched because the MIF levels tended to be higher in men with atherosclerosis, chronic obstructive pulmonary disease, and hypertension, therefore, it's questionable whether it is possible to achieve a control group consisting of 70-year old men without atherosclerosis including subclinical atherosclerosis (see Pan et al. Discussion on pages 632-634). Therefore, it is difficult to decide what constitutes the "a person not predetermined to be subject to cardiovascular disease" and/or an apparently healthy individual to practice the claimed methods.

Furthermore, Church et al. (International Journal of Obesity 2005. 29:675-681), in a study related to obesity, MIF serum concentration and weight loss with 71 severely obese participants, teach that elevation of circulating MIF concentrations are not uniform across individuals; only small percent of the obese participants have elevated circulating MIF concentration (see entire document, particularly Figure 1 on page 676); and it is not clear why some obese individuals have an elevated MIF while others do not; factors such as weight, waist girth, C-reactive protein or any of the cardiovascular disease risk factors are not associated with elevated MIF (see Discussion on pages 679-680).

Moreover, van Dielen et al. (The Journal of Clinical Endocrinology & Metabolism 2004. 89(8):4062-4068) show that MIF levels in morbidly obese individuals are low, and increase post gastric bypass surgery with decreasing body weight (see entire document, particularly Figure 2A on page 4064 and Discussion on pages 4065-4067). These results are clearly opposite to the disclosure of the instant specification in that the obese individuals have increased serum MIF level (see Examples on page 5-6 of the instant specification).

In addition, the instant method encompasses prescribing for the person a cardiovascular treatment modality in accordance with the test MIF (e.g. in lines 8-9 of the claim 1). However, the instant specification does not appear to disclose what treatment modality is prescribed.

In addition, the instant method encompasses “characterizing the individual’s risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third risk values different from said first and second risk values”: However, the instant specification does not appear to disclose how the third risk values are established from the first and second risk value and what constitutes third risk values.

In conclusion, there is insufficient objective evidence that the skilled artisan would be able to determine cardiovascular risk in a person not predetermined to be subject to cardiovascular disease and/or an apparently healthy individual by accessing MIF concentration given that high serum MIF levels have been described in a variety of diseases and it does not appear a proper control group can be achieved.

In view of the lack of predictability of the art to which the invention pertains, working examples, the state of the art teachings, undue experimentation would be required to practice the claimed invention.

8. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record set forth in the previous Office Action mailed 07/14/2006.

This is a *Written Description*, New Matter rejection.

Applicant's arguments filed 09/10/2006, have been fully considered but have not been found persuasive.

Applicant argues that the determined MIF concentration is a "test" and "compared-to value" or "predetermined value" is a "control". Therefore, The terms "a test MIF concentration" and "a control MIF concentration" have support in the specification, thus they are not new matters.

This is not found persuasive for following reasons:

Contrary to applicant's assertion, the specification the terms "a test MIF concentration" and "a control MIF concentration" in claims 1-19 and the phrase "not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk" as recited in claims 1-6 are not supported by the original disclosure or claim as filed.

Thus, the Written Description, New Matter rejection is adequate because applicant claims subject matter that was not adequately described in the specification as filed. New or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement.

Here, the instant specification only discloses obtaining a level of MIF expressed as “MIF concentration” and comparing the level to a “predetermined value” (see page 3 of the instant specification). However, the specification does not provide sufficient support for “a test MIF concentration”, “a control MIF concentration”, and “not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk”.

Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 and 2 are rejected under **35 U.S.C. 102(b)** because claims 1 and 2 are anticipated by Yabunaka et al. (Diabetes Care. 2000. 23;2:256-258) for reasons of record set forth in the previous Office Action, mailed 04/17/2006.

Applicant's arguments have been fully considered, but have not been found persuasive.

Applicant argues that the instant claim 1 recites a method of determining cardiovascular risk in a person not predetermined to be subject to cardiovascular disease. The claim requires at least two steps:

a first step of determining a test MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person, wherein an elevated test MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk; and

a second step selected from the group consisting of: (a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration; (b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration; and (c) making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay.

Yabanuka et al. neither teach nor suggest the claimed two-step method.

Further, applicant argues that Yabanuka et al. teach that MIF is not a specific disease marker but a nonspecific marker for illness in general.

This is not found persuasive for following reasons:

Contrary to applicant's assertion, Yabanuka et al. compare the concentration of serum MIF in type 2 diabetic patients to those normal healthy control subjects and assign a person cardiovascular risk metric (type II diabetes) in accordance with the test MIF concentration by comparing MIF in type 2 diabetic patients with that in normal control subjects.

In response to applicant's arguments that the reference fails to meet the claimed two steps, it is noted that during patent examination, the pending claims must be given the broadest reasonable interpretation.

In this case, Yabunaka et al. clearly anticipate the first step of determining a test MIF concentration and comparing the test MIF with a control MIF concentration not associated with cardiovascular risk.

Regarding the second step for the claimed methods, it is noted that claim 1 recites the second step being “wherein the method further comprises a step selected from the group consisting of (a), ... (b).... And (c)”; thus, claim 1, when given the broadest reasonable interpretation, would be anticipated by the teachings of Yabunaka et al. because the prior art teaches the first step of first step of determining a test MIF concentration and comparing the test MIF with a control MIF concentration not associated with cardiovascular risk, and the second step of assigning the person a cardiovascular risk metric in accordance with the test MIF concentration, especially given that it is not clear what constitutes the “cardiovascular risk metric” (see discussion above in Section 5(B)).

Therefore, the reference teachings anticipate the claimed invention.

Regarding applicant’s arguments that Yabanuka et al. teach that MIF is not a specific disease marker, see discussion in Section 7 above.

11. Conclusion: no claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.


Art Unit: 1644


Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chun Crowder, Ph.D.

Patent Examiner

November 17, 2006


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